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PEDIATRIC HYPERTENSION (B FALKNER, SECTION EDITOR)

Predictors and Consequences of Pediatric Hypertension: Have Advanced Echocardiography and Vascular Testing Arrived?

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Abstract
Purpose of Review Pediatric hypertension is relatively common and associated with future adult hypertension. Elevated blood pressure in youth predicts future adult cardiovascular disease and blood pressure control can prevent progression of pediatric kidney disease. However, pediatric blood pressure is highly variable within a given child and among children in a population.
Recent Findings Therefore, modalities to index aggregate and cumulative blood pressure status are of potential benefit in identifying youth in danger of progression from a risk factor of subclinical phenotypic alteration to clinically apparent event.
Summary In this review, we advocate for the health risk stratification roles of echocardiographically assessed cardiac remodeling, arterial stiffness assessment, and assessment by ultrasound of arterial thickening in children and adolescents with hypertension.

Keywords Pediatric hypertension · Echocardiography · Left ventricular hypertrophy · Left atrial dilation · Strain · Pulse wave velocity · Carotid intimal-medial thickness

Introduction

Recent studies show the prevalence of elevated blood pressure (BP) in children to be nearly one in seven [1]. Previous studies demonstrate that BP in childhood predicts adult BP status [2]. Studies predominantly in males found that BP measured at matriculation into college at a mean age of 19 years or conscription into military service at the mean age of 18 years predicted arteriosclerotic cardiovascular disease (ASCVD) events and ASCVD mortality 20+ years into the future, respectively [3••, 4]. Similar data in younger pediatric subpopulations show hypertension to predict early mortality [5]. On the other hand, vicissitudes in childhood BP make the variability in measurements affect the predictive ability of a given measurement [6]. Moreover, population trends in rising pediatric obesity are met by declining pediatric blood pressure with contrasting effects from adiposity versus other secular factors [7–9]. Therefore, biophysical alterations in body tissues and organs may help catalog the accumulated insults of adverse BP in a given child. In this review, we defend cardiac remodeling, arterial stiffness, and arterial thickening as possible indices of target organ damage in pediatric hypertension.

Cardiac Remodeling: Left Ventricular Hypertrophy, Left Atrial Dilation, Strain

By first principles, cardiac afterload, including but not limited to systemic blood pressure, is linearly related to higher ventricular wall stress. By Laplace's law, the heart muscle will thicken over time to normalize the ventricular wall stress. Therefore, echocardiographic assessment of left ventricular (LV) mass even to the point of left ventricular hypertrophy (LVH) can reveal clues to the severity and chronicity of BP elevation. LV mass has also been observed to be significantly increased even in prehypertensive children compared to normotensive children, suggesting that this metric may have clinical utility in identifying patients at an earlier stage in their disease process [10]. Fortunately, LVH has also been observed to improve after adequate blood pressure control [11]. While some studies have cast the association between elevated BP and LVH into doubt on balance LVH is widely accepted to be

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an index of chronic exposure to elevated BP [12, 13]. Additionally, other factors confound the relationship of LV mass to hypertension: LVMI (LV mass index) has been shown to correlate with BMI in pediatric patients [12, 14] and some studies have suggested that while both childhood hypertension and obesity and are contributors to adulthood LV mass, childhood obesity is the stronger predictor of the two [15, 16]. Reference ranges for LV mass measurements normalized to lean body mass in pediatric patients have recently been published [17], which may serve as a more accurate means of indexing LV mass measurements to body size to truly identify patients with hypertrophy out of the expected ranges for age and size. Therefore, LVH has cross-sectional, longitudinal, and interventional data supporting the use of LVH as a modifiable index of chronic and/or severe BP elevation.

Another established echocardiographic finding associated with hypertension is dilation of the left atrium (LA). While also a finding in other cardiac pathologies, LA enlargement can also result from decreased LA emptying due to impaired LV compliance secondary to systemic hypertension. The reported prevalence of LA dilation in hypertension has varied, with a recent pooled analysis of adult studies suggesting that this finding was a common feature of hypertensive adults, seen in approximately 32% of patients [18]. LA dilation has also been observed in pediatric patients with hypertension [19, 20], with one study reporting a prevalence of 51% [19]. Similar to LVH, there is also a significant association that has been found between pediatric obesity and LA enlargement [19–21]. Two large adult studies associated LA diameter to an increased incidence of cardiovascular events such as myocardial infarction, heart failure, stroke, and death [22, 23]. Furthermore, young adults without traditional and lifestyle risk factors for cardiac disease were found to have smaller LA dimensions; this is concordant with the finding that lifestyle characteristics aid in preventing ASCVD events [24]. Therefore, while the association between obesity and LA enlargement remains a confounding factor, the assessment of LA volume remains a useful tool in the assessment of pediatric hypertension.

Strain echocardiography represents a new imaging technique with the potential to provide further insights into the evaluation of pediatric hypertension. Using the tracking of acoustic speckles in the myocardium during echocardiography, regional deformation of the myocardium can be assessed over the course of an entire cardiac cycle and quantified as a change in dimension over the cycle relative to the dimension at rest [25•]. Strain may give more sensitive measurements of adaptive functional changes prior to frank structural changes. Numerous studies have emerged detailing the strain patterns in health and various disease processes, including systemic hypertension. Several studies have demonstrated the LA to be a valuable target for strain imaging in hypertension, with lower peak LA strain values being observed in hypertensive patients compared with healthy individuals [25•]. LA strain has also been able to differentiate normal individuals from those with masked hypertension, defined as normal BP readings in the office environment but elevated 24-h ambulatory BP [26]. Other research has detailed abnormal LA strain characteristics in the setting of nighttime hypertension [27–29]. Perhaps, most interesting are studies that have demonstrated abnormal LA strain in hypertensive individuals prior to any other evidence of myocardial dysfunction (e.g., LA enlargement and LV ejection fraction) [30]. LA characteristics are now becoming a focus of investigation in pediatric strain imaging as well, with research demonstrating altered strain patterns in pediatric patients with LA dilation compared to patients with normal atrial size [31]. Strain imaging has also been applied to pediatric hypertension, albeit thus far studies have mainly focused on LV strain, which has been found to be decreased in the context of systemic hypertension [32, 33]. Certainly, further research is needed on strain echocardiography in the evaluation of pediatric hypertension.

Echocardiography has been incorporated into the most recent American Academy of Pediatrics (AAP) Clinical Practice Guideline for screening and management of high BP in children and adolescents [34••] in several ways. Given the low sensitivity and poor positive predictive value of electrocardiograms to screen for LVH, it is currently recommended that echocardiography be performed in lieu of an electrocardiogram should LVH as a sequela of hypertension be suspected. Additionally, at the time of initiation of pharmacologic therapies for a child with diagnosed hypertension, echocardiography is recommended in order to characterize any effects longstanding hypertension may have had on the myocardium. Specifically, the AAP recommends assessment of LV mass, LV geometry, and cardiac function using echocardiography. Finally, serial echocardiograms have also been incorporated into the guidelines as a means of screening for worsening cardiac sequelae as a result of continued hypertension [34••]. Unfortunately, the AAP is only able to provide a moderate level of recommendation for these uses of echocardiography in the evaluation of pediatric hypertension given the lack of large, multinational or multicenter studies when compared with the body of adult literature on the subject. The AAP recommendations are also limited regarding the classification of LVH due to lack of available data on the subject: LVH in boys is defined as > 115 g/BSA and in girls is defined as > 95 g/BSA; however, these thresholds are above the 95th percentile for LV mass in population-based distributions. The significance of a LV mass between the cutoff for LVH defined by the AAP and the 95th percentile for sex is unclear. Nevertheless, the recommendation for echocardiography as part of an evaluation for pediatric hypertension is an important component of the AAP Clinical Practice Guidelines and will lead to further data on the cardiac sequelae of this disease process.

Arterial Stiffness: Pulse Wave Velocity

Arterial stiffness measures attempt to capture the tissue characteristics of the artery/arteries measured as indicative of ultrastructural changes caused by relevant factors. While various indices have been used including pulse pressure, Young's modulus, characteristic impedance, forward pulse wave amplitude, distensibility index, and augmentation index, the current gold standard measurement is pulse wave velocity (PWV). PWV represents the speed at which the pulse wave produced by left ventricular systole is propagated throughout the arterial tree, with stiffened arteries exhibiting faster propagation of this impulse. Conceptually, PWV is the distance traveled by the impulse between two measured sites divided by the time taken to travel between those sites, giving distance divided by time, i.e., velocity. Conventionally, the difference in time delay between the ECG R-wave and the arrival of the arterial pulse waveform at two different sites determines the time for impulse travel. Next, the distances are measured either by convention from the suprasternal notch to the sites of arterial measurement or directly measured if the distance is assessed by imaging [35•, 36••]. Therefore, PWV can be assessed using any artery available for palpation or imaging; some methods for PWV include carotid-femoral [37–43], carotid-toe [44], or brachial-femoral [45] measurements, or whole-body impedance cardiography [46] and brachial oscillometry [47, 48•]. At the current time, carotid-femoral pulse wave velocity (CFPWV) is the gold standard measurement.

Unfortunately, the 2017 American Academy of Pediatrics Clinical Practice Guidelines [34••] recommends against the routine assessment of PWV in youth with suspected hypertension. The committee's key concerns were a lack of data to assess normal versus abnormal, lack of racial and ethnic heterogeneity in ostensibly normative data, and the variation between different forms of PWV measurement. Another concern is that other factors such as elevated BMI or insulin resistance are associated with increased PWV, diluting the specificity of PWV for BP-driven change [40, 47, 49].

Arguing against the committee's skepticism are several considerations. First, it is clear that pediatric BP, in general, is subject to a lack of health outcome relevant thresholds for normal versus abnormal. Normative data does exist to determine reference values for PWV in two large pediatric cohorts in order to generate distribution based thresholds rather than outcome-based thresholds, in a manner analogous to BP [37, 48•]. Second, while these cohorts are largely from a European population which may limit their generalizability, there are not yet data to conclude that race/ethnicity-based variation in PWV should be accounted for in normative thresholds any more than BP thresholds. It is unclear why PWV should be subjected to more stringent standards generation, and it is moreover dubious that race/ethnicity-specific thresholds would find favor among treating clinicians. Nonetheless, race/ethnicity inclusive normative data is eagerly awaited and of unambiguous benefit. Third, previous data has indeed compared and confirmed the interoperability between various PWV measurement types and lack of operator-dependence, both of which make PWV an attractive testing modality [50]. Fourth, while PWV may not be specific to BP-driven change alone, neither is sine qua non of target organ damage, LVH. Indeed, key longitudinal cohorts demonstrate the relative strength of longitudinal association between childhood adiposity versus BP on adulthood LVH, and both are of relevance [51]. Therefore, the lack of specificity for BP per se is not a hindrance to the assessment of target organ damage.

In addition to these methodological counterarguments, the most critical domain arguing against relegation of arterial stiffness is relevance to actual health. Aortic stiffness is a powerful predictor of future cardiovascular and all-cause mortality in general population as well as hypertensive adults, even after adjustment for classic cardiovascular risk factors, indicating it has explanatory power independent of usually measured risk factors [52•, 53]. Arterial stiffness is a key correlate of pediatric hypertension [7, 54]. Multiple studies demonstrate that as PWV increases, arterial stiffness also increases [40, 41, 43–45, 47]. These changes in arterial stiffness have been found to manifest in a linear fashion, even at prehypertensive blood pressure levels [41, 45]. Even taking other known cardiovascular risk factors such as BMI and diabetes into account, pre-hypertension and hypertension were both found to be independently associated with increased PWV in pediatric patients [44, 45]. Recent studies have also found an association between multiple ambulatory BP measures and PWV, consistent with PWV representing signs of vascular injury secondary to longstanding elevations in blood pressure [42, 43]. In findings from both the Cardiovascular Risk in Young Finns Study [46] as well as the Beijing Blood Pressure Cohort Study [38], hypertension in childhood was associated with an increased risk of an elevated PWV in adulthood. The Cardiovascular Risk in Young Finns Study also highlighted that pediatric hypertension that had resolved by adulthood attenuated the increased risk of elevated PWV in adulthood [46]. Thus, PWV in youth is a correlate of current hypertension, childhood BP predicts higher PWV in adulthood, adult PWV, in turn, predicts future CVD events and normalization of BP from childhood to adulthood attenuated PWV worsening. Thus, PWV could prove to be of great benefit in identifying at-risk individuals whose arteries have been stiffened in adaptation, or maladaptation, to elevated BP. Publication of standardized protocols for evaluating pediatric patients with hypertension using PWV may provide guidance to future studies and help alleviate the heterogeneity in studies observed thus far. PWV should be included as a valuable tool in the evaluation of pediatric hypertension.

Arterial Thickening: Carotid Intimal-Medial Thickness

By Laplace's law, higher distending pressure in the vessel induces thickening of the vessel wall so as to reduce transmural wall tension. Therefore, one assessment of blood pressure-related vascular health is thickening of the arteries, measured most commonly as carotid intima-media thickness (cIMT). Adequately, high-spatial resolution ultrasonography of the common carotid or its branches is performed and the combined thickness of the intimal and medial layers is measured [36••, 55, 56•]. Despite the conceptual elegance of cIMT, the 2013 ACC/AHA guidelines for assessment of cardiovascular risk in adults [57] recommended against the use of cIMT as routine screening for arteriosclerotic cardiovascular disease risk stratification. In contrast, the American Society of Echocardiography (ASE) advocates for the use of cIMT in the evaluation of cardiovascular risk [55]. In children, the American Academy of Pediatrics 2017 Clinic Practice guideline recommended against cIMT [34••] while the Association for European Paediatric Cardiology (AEPC) was generally supportive [58••].

Conflict in expert guidelines is predicated on two major stumbling blocks. One hindrance to cIMT acceptance is a lack of agreement between measurements. This discordance appears to stem from interobserver variability and dependency on variables such as ambient lighting, neck position, and angle of interrogation. Standardization of the techniques for measuring the carotid intima-medial thickness (cIMT) continues to be an active focus of research and discussion in the adult literature, with a consensus document (the "Mannheim Consensus") on ultrasonography techniques published in 2004 and subsequently updated in 2006 and 2011 [56•]. An AEPC working group recommended using at least a 7 MHz probe, scanning both carotid arteries, assessing cIMT at end-diastole over a 10-mm distance of the common carotid artery just before the start of the carotid bulb, ensuring the angle of insonation was perpendicular to the common carotid artery, measuring the leading edge-to-leading edge of the arterial layers, and using the definition of the top age-sex referenced quartile as abnormal [58••]. Assignment of normative values is now likely derivable given several published reference values in children from around the globe [59–63, 64•]. However, patient selection and small absolute numbers within age-sex-race/ethnicity substrata indicate further studies are needed to produce more robust cIMT reference ranges for healthy children. Another possible approach would be an extrapolation from adulthood thresholds back to pediatric levels based on normative thickening velocity.

The second key obstacle to cIMT use is repeated studies showing limited utility of additional risk stratification from cIMT measures beyond classic arteriosclerotic cardiovascular disease (ASCVD) risk factor measurement alone [65]. Specifically, constructed studies were able to demonstrate that while the presence of distinct plaques gave additional risk prediction over traditional risk factors; general thickness of cIMT was associated with ASCVD risk factors but not substantially additive to those risk factors [66]. However, when viewed from the pediatric life course perspective, these findings are actually a strength, not a weakness. BP in children varies over the life course and even at a single visit. Moreover, children are also prone to reactive ("white coat") hypertension. So, while a given measured BP in adults may be deemed representative of a stable if not soon-to-worsen phenotype, a child's BP may fluctuate substantially. In that context, recent studies have observed a positive correlation between systolic blood pressure and cIMT in children [67, 68, 69•]. When normotensive children are compared with children with hypertension, those with hypertension were found to have significantly higher cIMT values [70, 71]. Multiple studies [72–75] demonstrate that hypertensive children have higher cIMT measurements when compared to normotensive children, even when BMI and other anthropomorphic data are taken into account, contrary to earlier studies [76]. Other investigators have shown cIMT was associated with left ventricular hypertrophy, independent of age, sex, or BMI [77]. Most intriguing, cIMT appears to be temporally antecedent to other target organ damage wherein ambulatory blood pressure monitor-determined reactive and sustained hypertensive children both have thickened cIMT but only sustained hypertension had LVH [78]. Equally intriguing is longitudinal cohort data demonstrating that improvement in BP from childhood to adulthood attenuated thickening of cIMT [79].

Therefore, cIMT may provide excellent data for the assessment of BP status in children. Provided cIMT is measured and classified appropriately, cIMT may "summarize" true BP insults to the vessel wall as accumulated over time in children with fluctuating blood pressure. Next, the measured cIMT may be postulated as target organ damage preceding future BP-derived consequences, especially when referenced against either the cross-sectional normative value in children or extrapolated against adult values related to outcome coupled with thickening velocity. Finally, cIMT may reflect BP consequences both in terms of deleterious BP insults and salutary BP improvement. BP management should include cIMT assessment.

Conclusion

Primordial and primary preventive cardiology is undergoing significant changes with regard to the evaluation of pediatric hypertension and its end-organ effects. New imaging modalities have the potential to transform the field, potentially allowing for earlier diagnosis, identification of individuals at higher risk for poor outcomes, and a more thorough

assessment of responses to therapies. However, still much research into these new imaging modalities remains to be done. While the AAP Guidelines wisely advise restraint against a broad application of these emerging technologies, given the potential benefit to our patients, further study of the use of advanced imaging in pediatric hypertension should be strongly considered by all.

Compliance with Ethical Standards

Conflict of Interest Kyle D. Hope and Justin P. Zachariah declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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